

Supplemental Vitamin A Retards Loss of ERG Amplitude in Retinitis Pigmentosa

"Based on these findings and the analysis of decline of ERG [electroretinogram] amplitude as a function of total vitamin A intake, it is recommended that most adult patients with the common forms of retinitis pigmentosa take a supplement of vitamin A, 15 000 IU/d, under the supervision of an ophthalmologist and avoid the use of high-dose supplements of vitamin E, such as the 400 IU/d used in this trial.¹"

These words conclude the report of a clinical trial published in this issue of the ARCHIVES that was designed to evaluate the effects of nutritional supplements of vitamins A and E on the natural course of retinitis pigmentosa. This study is a tour de force in experimental design, execution, and statistical analysis. The investigators deserve congratulations on the successful completion of this ambitious, rigorous, and interesting study.

See also pp 754 and 761.

Retinitis pigmentosa can be a devastating disease for the patient who suffers night blindness, progressive visual field loss, and eventually loss of central vision. There is no cure for retinitis pigmentosa, and patients are in constant search of hope. Therefore, when interpreting the intriguing results of this clinical trial, it is important to use caution and to avoid drawing unwarranted conclusions that could lead to unreasonable expectations by patients. Despite our admiration of the design and execution of this study, we raise concerns about the conclusions and with the recommendations put forward by the authors. Specifically, we have three areas of concern: (1) The study did not demonstrate significant benefit for any measure of visual function. (2) The significant effect observed with the cone electroretinogram (ERG) has additional explanations not related to slowed disease progression. (3) The long-term systemic and/or toxic effects of supplemental vitamin A are unknown.

VISUAL FUNCTION OUTCOME

The conclusion of this study that high dosages of vitamin A are beneficial for retinitis pigmentosa is based entirely on one aspect of the cone ERG. In considering the outcomes of this study, it is important to note that the investigators did not demonstrate statistically significant benefit of treatment for any aspect of visual function. We use the term *visual function* to refer to psychophysical measures that quantify the patient's

visual symptoms. For example, visual acuity corresponds to resolution, contrast sensitivity corresponds to object visibility, dark-adapted thresholds correspond to night vision, and perimetric measures of luminance difference thresholds correspond to the visual field. Although physiological measures of retinal function, such as the ERG, might be expected to be correlated with visual function, they are not direct measures of visual function. Several other variables, such as the electrical properties of the retina, electrical properties of the eye, or nonneural sources of bioelectric activity, can reduce the correlation between electrophysiological measures and actual visual function.

In this study, the visual function outcome measures were kinetic perimetry and visual acuity. No measures of dark-adapted thresholds were included. For visual field measures, the investigators reported nonsignificant differences in the rates of loss of that portion of the visual field "contiguous to center." (The trend was mixed. As with the ERG results, the high-dosage vitamin A group had the lowest rate of loss and the high-dosage vitamin E group had the highest rate of loss. However, unlike the ERG results, the control [ie, trace or placebo] group had a lower rate of loss than that recorded for group A + E.) Curiously, the *total* visual field area for patients with retinitis pigmentosa in the control group showed no significant decline over the 4-year course of the study (0.4% per year, $P=.50$). This observation stands in marked contrast to our finding that the total visual field area in retinitis pigmentosa is lost at the rate of 16% per year *once progressive visual field loss begins*.² The failure to observe progressive visual field loss for the Goldmann V-4-e target in the control group of the present study suggests that visual field loss for this stimulus had not started for many of the patients participating in this study. For both the treatment and control groups, the data of patients with retinitis pigmentosa who had no visual loss over the follow-up period were added to the data of patients who did have visual field loss over the same interval. Adding data of patients who did not experience progressive visual field loss to the data of those who did can only result in underestimates of the average rate of loss for each group. It is possible that more patients who did not yet have measurable visual field loss were randomly allocated to the vitamin A group than were allocated to the other groups. Such an allocation bias would produce an artifactually lower rate of loss for the vita-

min A group. On the other hand, there could have been beneficial effects of treatment that went undetected with visual field measures because patients without measurable visual field loss diluted the rate estimates for all groups.

Although typically visual acuity loss in retinitis pigmentosa is not clinically significant until later in the course of disease progression,³ careful laboratory measures of visual resolution do reveal losses of visual acuity even in the early stages of retinitis pigmentosa.⁴ No statistically significant differences in the rate of loss of visual acuity were seen between the different groups in the present study. However, there is a disturbing trend in the data: the greatest rate of loss occurred in the high-dosage vitamin A group, the lowest rate of loss occurred in group A+E, and the same intermediate rate of loss was recorded for the high-dosage vitamin E and control groups. These results, if they had achieved statistical significance, would have led to the conclusion that high dosages of vitamin A for retinitis pigmentosa are detrimental to visual acuity.

The investigators argue that the ERG can serve as a surrogate for visual function measures because they demonstrate a relationship between cone ERG amplitude and patients' reports of disabilities in some activities related to "quality of life." To the extent that patients with greater loss of visual function are likely to have smaller ERGs than patients who have little loss of visual function, the observed relationship is not unexpected. However, observing a positive relationship between ERG amplitude and the ability to perform routine daily activities across a large sample of patients is not sufficient evidence to conclude that the rate of loss in ERG amplitude corresponds to the rate of disease progression. The ERG amplitudes used to establish the relationship with the ability to perform routine activities covered at least a 13-fold range (<0.34 to $>4.53 \mu\text{V}$). In comparison, over the 4-year course of the study, the average ERG amplitude for individual patients changed over a 1.4- to 2.4-fold range (see Fig 5 in the article by Berson et al). Conclusions that apply to the large range of ERG amplitude across patients are not necessarily valid over the much smaller range of change in ERG amplitude for individual patients.

ALTERNATIVE EXPLANATIONS FOR THE ERG RESULTS

Although changes in neural retinal function due to the progression of retinitis pigmentosa are likely to cause changes in the ERG, one cannot conclude that change (or lack of change) in the ERG necessarily reflects a change (or lack of change) in neural retinal function. Because the conclusions of this study are drawn from ERG measures, it is important to critically evaluate the ERG results and discuss some possible alternative explanations for the outcome.

The 30-Hz flicker ERG, the significant outcome measure of this study, is a very small potential in retinitis pigmentosa. The normal flicker ERG has an amplitude of $100 \mu\text{V}$ or more. With conventional modern recording techniques, ERG amplitude values less than $3 \mu\text{V}$ usually are considered indistinguishable from

background electrical signals generated by eye movements, muscle activity, brain activity, environmental electromagnetic fields picked up by the electrode, etc (this background is called noise).

Patients with retinitis pigmentosa were considered eligible for this study if the pretreatment 30-Hz flicker ERG amplitude was $0.12 \mu\text{V}$ or greater. Signals this small can be recorded only if special signal processing techniques are employed. However, these techniques require caution when interpreting data. The techniques employed in this study (narrow-band filtering and signal averaging) always produce signals that look like 30-Hz sine waves, whether the signals are generated by retinal activity or by background noise. Only the amplitude and phase of the sine wave can vary, but neither the frequency nor the shape of the waveform can change. Because the sum of the ERG and background noise also produces a 30-Hz sine wave, it is not possible to tell from the recording how much of the signal represents an ERG response and how much is noise.

If the patient's ERG signal is small relative to the magnitude of the background noise, the recorded response will have an important noise component. Noise is random and may be idiosyncratic. It depends on individual differences among patients in physiological parameters as well as on the activity of electromagnetic field generators in the local environment. Because noise is independent of the ERG signal, the average noise contribution to the recorded signal would not be expected to change with progression of retinitis pigmentosa. The more noise there is in the signal, the less the recorded signal will change over time, even if the ERG part of the signal progressively decreases. In the extreme case, if the recorded signal is mostly noise, there will be no change over time in the signal even though the retina is continuing to degenerate.

This problem of noise contamination was recognized by the authors. They observed in their sample of patients with retinitis pigmentosa that those in the control group with signal amplitudes less than $0.68 \mu\text{V}$ exhibited no measurable rate of decline in amplitude over the 4-year follow-up. Thus, any signal smaller than $0.68 \mu\text{V}$ is likely to be entirely noise. On that basis, data from 38% of the original 575 patients were excluded for purposes of a "higher-amplitude cohort" subgroup analysis. However, signal values above $0.68 \mu\text{V}$ still contain noise, and the noise will dilute the estimates of the rate of disease progression made from signal amplitude measures.

The conclusions of the study are based on estimated relative annual rates of change in ERG amplitude (ie, the slope of the line fitted to the log of signal amplitude as a function of time). The assumption of the analysis is that the natural course of loss of ERG amplitude in retinitis pigmentosa follows an exponential decay; this assumption, although reasonable based on extrapolation from visual field data,² has never been proven for the ERG. Nevertheless, whatever the dynamics of ERG loss, as the ERG signal is reduced relative to the background noise, the rate of change computed for the recorded signal amplitude will be less than the actual rate of change in the ERG signal (in the extreme case,

the computed rate of change will be zero when the recorded signal is all noise).

The main observation of the study is that patients given high dosages of vitamin A had slower rates of change in ERG amplitude than those recorded for patients given low dosages of vitamin A. However, a curious and unexplained observation is that the placebo group in this study had a rate of change (7.1% per year) that was less than half that reported for a similar group of 86 patients with retinitis pigmentosa (18.5% per year) who participated in a prior natural history study conducted by the same laboratory.⁵ One plausible explanation for this discrepancy is that, due to the luck of the draw or to self-selection, the ERG signal-to-noise ratios were greater for patients in the earlier natural history study than for patients who participated in the present study.

Because of noise in the ERG, the results of the present study could have several explanations. First, as suggested by the study's authors, vitamin A supplements may actually slow the rate of progression of retinitis pigmentosa. If so, noise contributions to the measured ERG would lead to underestimation of the magnitude of the difference in rate of progression between the high- and low-dosage vitamin A groups. Thus, if there were a real effect of treatment, it would be larger than that observed in the present study. Second, vitamin A may increase the background noise level by altering nonretinal physiological parameters (remember that the signals are very small to begin with). This effect would result in greater noise in the ERG for the high-dosage vitamin A groups than for the low-dosage groups. Thus, even if the rate of disease progression were identical for all groups, the increased noise would result in an *apparent* lower rate of change in the high-dosage vitamin A groups than would be measured in the low-dosage groups. Third, vitamin A might change the electrical properties of the eye (eg, through changes in the tears, cornea, or conjunctiva), which would affect the amplitude of the signal picked up by either the active or reference electrode. Increased signal strength from pure electrical effects could partially offset decreasing signal strength accompanying disease progression to produce a measured slower rate of change in the vitamin A group. Again, the difference would be due to an artifact of vitamin A, not to any effect vitamin A had on the natural course of retinitis pigmentosa. Fourth, by chance, more patients with low signal-to-noise ratios might have been allocated to the high-dosage vitamin A groups than to the low-dosage vitamin A groups. Randomization does not guarantee balance, and there is no indication that the investigators attempted to balance the allocations of patients on the basis of pretreatment ERG signal-to-noise ratios (the pretreatment log_e amplitude means and SEs are in close agreement for the four groups; however, amplitude reflects the *sum* of ERG signal and noise). Such an allocation bias would result in a measured slower rate of change in the high-dosage vitamin A group due to noise dilution of the rate estimate, even though there might be no actual change in the rate of loss.

We believe that the important observations of this study are strictly limited to the ERG measures. Without a better understanding of the reason for the ERG effects, we cannot conclude from the data that supplemental vitamin A alters the natural course of retinitis pigmentosa.

RISKS OF VITAMIN A SUPPLEMENTATION

Little is known about the systemic effects and/or toxicity of long-term (over decades) supplementation with vitamin A, particularly when taken through childhood and pregnancy. The investigators saw no toxic or systemic effects in their study patients over the relatively short follow-up period, but their initial concern was not unwarranted; young and pregnant patients were specifically excluded.

Although there are several hundred publications on the subject of acute and chronic vitamin A toxicity in humans from very large dosages of vitamin A, it is not possible to estimate the effect of smaller dosages that might produce more subtle changes when used over a long period of time. For very high dosages, 20 to 200 times the recommended daily allowance (ranging from 1400 IU/d in infants under age 6 months to 6000 IU/d in a lactating adult), systemic toxic effects of particular concern may include signs and symptoms of increased intracranial pressure, hepatomegaly, bone changes in children, and elevated blood lipid levels.⁶

A fatal case in an adult attributed to hypervitaminosis A occurred in a 62-year-old with hemolytic anemia who took up to 17 capsules daily of 15 000 IU each (up to 255 000 IU/d total) for 5 years. Another fatal case was reported in an infant whose parents misunderstood the prescribed dosage. Teratogenesis has been shown to occur in animals at high dosages; in humans, five cases of birth defects have been reported associated with hypervitaminosis A, but a cause-and-effect relationship has not been established. These and other cases are reviewed in a recent publication.⁷

For more detailed information and reviews, ophthalmologists, internists, pediatricians, and patients with retinitis pigmentosa who are considering vitamin A supplementation based on the current report by Berson et al may wish to consult the information in *The Safe Use of Vitamin A: A Report of the International Vitamin A Consultative Group* (available for \$3.50 from the Nutrition Foundation, 1126 16th St NW, Washington, DC 20036).⁶

CONCLUSIONS

Given the somewhat speculative nature of the possible clinical benefits of vitamin A supplementation for retinitis pigmentosa, the potential risks of this therapy take on greater significance. We would exercise caution in *prescribing* supplemental vitamin A to patients with retinitis pigmentosa. Our recommendation is to inform patients of the results of this study and of the potential risks of supplemental vitamin A and to caution them that the results of the study apply only to the ERG and may not be generalizable to the loss of visual function. Despite the inevitably high expecta-

tions, we hope that patients will acquire a balanced view of the potential risks, benefits, and alternatives before deciding with their physicians whether or not to proceed with vitamin A supplementation.

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References

1. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol*. 1993;111:761-772.

2. Massof RW, Dagnelie G, Benzsawel T, et al. First order dynamics of visual field loss in retinitis pigmentosa. *Clin Vis Sci*. 1990;5:1-26.
3. Madreperla SA, Palmer RW, Massof RW, Finkelstein D. Visual acuity loss in retinitis pigmentosa: relationship to visual field loss. *Arch Ophthalmol*. 1990;108:358-361.
4. Alexander KR, Derlacki DJ, Fishman GA, Szlyk JP. Grating, vernier, and letter acuity in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1992;33:3400-3406.
5. Berson EL, Sandberg MA, Rosner B, et al. Natural course of retinitis pigmentosa over a three-year interval. *Am J Ophthalmol*. 1985;99:240-251.
6. Bauernfeind JC. *The Safe Use of Vitamin A: A Report of the International Vitamin A Consultative Group*. Washington, DC: The Nutrition Foundation; 1980.
7. Bendich A, Langseth L. Safety of vitamin A. *Am J Clin Nutrition*. 1989; 49:358-371.

How Shall Research in the Treatment of Retinitis Pigmentosa Proceed?

Retinitis pigmentosa (RP) is a group of hereditary eye diseases, characterized by retinal degeneration, that have no known cure.¹ The prevalence of RP is approximately one in 3000 persons worldwide. The initial symptom of RP is night blindness that usually begins during adolescence. Patients next experience constricted visual fields and eventually a profound loss of peripheral vision. In the course of the eye's deteriorating condition, abnormal pigmentation characteristically accumulates, starting usually in the mid-peripheral retina. Typically by middle age, the patients are legally blind. The pattern of RP recurrence in an individual's family indicates whether the genetic type is X-linked, recessive, or dominant.¹

Ideally, research in RP treatment should begin when all the variations on the pathogenic chain of events resulting in the phenotype have been identified. Although RP research has not arrived at this point, a considerable body of knowledge about some of the critical cellular and molecular events that lead to the RP phenotype has been produced. Furthermore, animal models that simulate the RP condition in humans are now available for testing. Although molecular research into the etiology of RP continues, we, as researchers in this field, may have arrived at the point where research in the treatment of RP should begin.

An important step in studying—and ultimately treating—hereditary disorders like RP is the identification of the genetic lesions that lead to the phenotype. This degree of precision has been achieved recently for some forms of RP: namely those autosomal dominant RP (ADRP) types caused by mutations in the genes for the proteins designated *retinal degeneration slow* (*rds*)/peripherin and rhodopsin.² Because the rhodopsin gene is expressed only in rod photoreceptors and the *rds*/peripherin gene is expressed only in rod and cone photoreceptors, the actions of mutant genes that lead to ADRP are expected to appear initially on the photoreceptors. The degeneration of photoreceptors that characterizes ADRP is thus likely to be mediated by

cellular mechanisms that are intrinsic to the photoreceptors. For these forms of ADRP, then, the damage to or loss of photoreceptors precipitates the entire clinical course of the disease.

See also pp 751 and 761.

Although the genetic lesions that lead to some forms of ADRP are known, a common theme that emerges from research on the mutations identified in both the rhodopsin and the *rds*/peripherin genes is that other cellular mechanisms, not the genetic defect alone, cause degeneration of the photoreceptor cells. In the case of rhodopsin, for example, it is believed that its major, or perhaps only, function is to capture photons and thus initiate visual transduction.^{3,4} Since this function is highly specialized, rhodopsin does not play a direct role in cell maintenance or viability. Furthermore, a normal copy of the rhodopsin gene in ADRP patients suggests that the phenotype does not require a total loss of function in the rhodopsin gene. How, then, could a genetic defect in the rhodopsin gene cause the photoreceptors to degenerate? Other cellular mechanisms probably come into play; thus, the mutant molecules only trigger those mechanisms that eventually lead to rod photoreceptor degeneration. The demise of the rod photoreceptors, then, causes the subsequent events and symptoms characteristic of the disease, including the loss of cone photoreceptors.

While less is known about the *rds*/peripherin gene than the rhodopsin gene, the idea that cellular mechanisms other than the primary mutation itself play a critical role in photoreceptor degeneration appears equally applicable. Phenotypes caused by mutations in the *rds*/peripherin gene were first studied in *rds* mutant mice.⁵⁻⁸ In young animals that were homozygous for the *rds* mutation, the photoreceptors grew in the normal fashion up to the time when the outer segments should have developed, but failed to form; the